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HAMRE, SCHUMANN, MUELLER & LARSON, P.C.
P.O. BOX 2902
MINNEAPOLIS, MN 55402-0902

EXAMINER

MUMMERT, STEPHANIE KANE

ART UNIT

PAPER NUMBER

1637

MAIL DATE

DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary**Application No.**

10/583,706

Applicant(s)

MITANI ET AL.

Examiner

STEPHANIE K. MUMMERT

Art Unit

1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 April 2011.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 4/4/11, 4/5/11, 6/2/11

- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 4, 2011 has been entered.

Applicant's amendment filed on April 4, 2011 is acknowledged and has been entered. Claims 8-83 have been canceled. Claims 1-7 are pending.

Claims 1-7 are discussed in this Office action.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made FINAL.

Information Disclosure Statement – considered – with clarification requested

The information disclosure statement (IDS) submitted on March 15, 2010 and April 13, 2010 were filed in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Applicant's explanation and the concise explanation of relevance are appreciated. However, the concise explanation appears to be in conflict with the translation of the documents present on the respective IDS documents. For example, the concise explanation explains that "a suit for cancelling trial decision of Mukou... that was filed by Eiken Kagaku Kabushiki Kaisha (demandant)". The concise explanation also states that "the defendant explained in the suit for canceling trial decision of Mukou... that the demandant's arguments were technically wrong, and, the experimental data submitted by the demandant on January 19, 2010 was inappropriate" (p. 2 of remarks). It is noted that the translation of the brief documents list "Kabushiki Kaisha DNAFORM" as the "Demandee" and "Eiken Chemical Co., Ltd" as the Demandant. Is this information incorrect? Is the demandee equivalent to the defendant as argued in the concise explanation? Clarification is requested.

Previous Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rabbani et al. (EP0971039A2, published January 12, 2000) in view of David et al. (WO96/001327; January 1996). Rabbani teaches a set of primers for the amplification of a target (Abstract).

With regard to claim 1, Rabbani teaches a primer set comprising at least two primers that allows a target nucleic acid sequence to be amplified, wherein a first primer included in the primer set contains, in its 3' end portion, a sequence (Ac') that hybridizes to a sequence (A) located in the 3' end portion of the target nucleic acid sequence, and also contains, on the 5' side of the sequence (Ac'), a sequence (B') that hybridizes to a complementary sequence (Bc) to a sequence (B) that is present on the 5' side with respect to the sequence (A) in the target nucleic acid sequence (Figure 4, step 1 and 2, where the first primer includes a sequence F at 3' end complementary to the F' portion at the 3' end of the template, and a sequence E' that is complementary to the E sequence that is 5' with respect to F in the target; and where F and E are

equivalent to and in the same format and locations as the regions designated A, B, C, D in the template/target).

With regard to claim 2, Rabbani teaches an embodiment of claim 1, further comprising a third primer that hybridizes to the target nucleic acid sequence or the complementary sequence thereto, wherein the third primer does not compete with other primers for hybridization to the target nucleic acid sequence or the complementary sequence thereto (Figure 2, step 1, primer F, which binds to an extension product of the second primer of claim 1, including the folded sequence).

With regard to claim 3, Rabbani teaches an embodiment of claim 1, wherein in the first primer, when no intervening sequence is present between the sequence (Ac') and the sequence (B'), a ratio $(X-Y)/X$ is in a range of -1.00 to 1.00, where X denotes the number of bases contained in the sequence (Ac') while Y indicates the number of bases contained in a region flanked by the sequence (A) and the 30 sequence (B) in the target nucleic acid sequence, and when an intervening sequence is present bet the sequence (Ac') and the sequence (B') in the primer, a ratio $\{X-(YY')\}/X$ is in a range of -1.00 to 1.00, where X and Y denote the same as described above, and Y' indicates the number of bases contained in the intervening sequence (see Example 1, p. 21, paragraphs 117-118, where the first primer has an F region (corresponding to Ac') of 29 or 30 nucleotides and since there is no intervening sequence between F and E (corresponding to A and B), where the flanking region is 0 nucleotides. Therefore, $(X-Y)/X = (29-0)/29 = 1$).

With regard to claim 4, Rabbani teaches the second primer, the folded sequence (D-Dc') has a length of 2 to 1000 nucleotides (p. 21, paragraph 118, where the stem loop structure

depicted in Figure 4, where the basepair stems are 30 bp and 29 or 30 bp loops, leading to a folded sequence of approximately 90 bp).

With regard to claim 5, Rabbani teaches an embodiment of claim 1, wherein at least one primer included in the primer set has a solid-phase support or a site that can bind to a solid-phase support (p. 19, paragraph 103, where the primer includes a group that is useful for attachment of signal generating groups which can also be useful for binding to other formats, including a solid support).

Regarding claim 1, while Rabbani teaches a variety of secondary primers which could easily be combined with the first primer and while Rabbani teaches primers which when extended will form a stem or hairpin structure (see Figure 4, Figure 9), these primers do not have a fold-back portion precisely as claimed.

With regard to claim 1, David teaches a second primer included in the primer set contains, in its 3' end portion, a sequence (Cc') that hybridizes to a sequence (C) located in the 3' end portion of a complementary sequence to the target nucleic acid sequence, and also contains, on the 5' side of the sequence (Cc'), a folded sequence (D-Dc') that contains, on the same strand, two nucleic acid sequences that hybridize to each other (Figure 1, 2, 5, where the second primer includes a region P-P' which forms a folded sequence at the 5' end of the primer and a sequence S in the 3' end of the primer which hybridizes to the sequence S on the template).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the teachings of Rabbani to include the known alternative hairpin primer format of David to arrive at the claimed invention with a reasonable expectation for success. As noted above, while Rabbani does not teach the specific hairpin as claimed,

Figure 4 of Rabbani alone suggests a combination of primers which includes the first primer, as noted above and a second sequence at the opposite end of the template or extension product which includes a folded hairpin sequence. Further, as taught by Rabbani, "the initial primer or nucleic acid construct and the second primer or nucleic acid construct can be the same, or they can be different" (paragraph 43, p. 8). Considering this, it would have been obvious to one of skill to substitute in a variety of secondary primers of different sequence and structure than the initial primer described as the first primer in the invention claimed herein, including a particular hairpin primer as taught by David. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have extended the teachings of Rabbani to include the known alternative hairpin primer format of David to arrive at the claimed invention with a reasonable expectation for success.

Claims 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rabbani et al. (EP0971039A2, published January 12, 2000) in view of David et al. (WO96/001327; January 1996) as applied to claims 1-5 above in view of Pastinen et al. (Genome Research, 1997, vol. 7, p. 606-614). Rabbani teaches a set of primers for the amplification of a target (Abstract).

With regard to claim 5, Rabbani teaches an embodiment of claim 1, wherein at least one primer included in the primer set a site that can bind to a solid-phase support (p. 19, paragraph 103, where the primer includes a group that is useful for attachment of signal generating groups which can also be useful for binding to other formats, including a solid support).

Regarding claim 5, while Rabbani teaches a site for attachment to a solid phase support, Rabbani does not teach attachment to a solid phase support. Pastinen teaches attachment of primers to solid phase support prior to mini-sequencing reactions (Abstract).

With regard to claim 5, Pastinen teaches an embodiment of claim 1, wherein at least one primer included in the primer set has a solid-phase support or a site that can bind to a solid-phase support (p. 610, col. 2, where oligonucleotide primers were spotted onto a glass slide, attached by a 5' amino group).

With regard to claim 6, Pastinen teaches an embodiment of claim 5, wherein the solid-phase support is one selected from the group consisting of a water-insoluble organic polymer support, a water-insoluble inorganic polymer support, a synthetic polymer support, a phase transition support, a metal colloid, and a magnetic particle (p. 610, col. 2, where oligonucleotide primers were spotted onto a glass slide, attached by a 5' amino group).

With regard to claim 7, Pastinen teaches an embodiment of claim 5, wherein the site that can bind to a solid-phase support is selected from the group consisting of biotin, avidin, streptavidin, an antigen, an antibody, a ligand, a receptor, a nucleic acid, and a protein (p. 610, col. 2, where oligonucleotide primers were spotted onto a glass slide, attached by a 5' amino group).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have adjusted the teachings of Rabbani and David to include the attachment of primers to solid phase supports as taught by Pastinen to arrive at the claimed invention with a reasonable expectation for success. As taught by Pastinen, "mutations are detected by extending immobilized primers that anneal to their template sequences immediately adjacent to the mutant nucleotide positions with single labeled dideoxynucleoside triphosphates using a DNA polymerase" (Abstract). Pastinen also teaches, "Our results show that single-nucleotide primer extension is an excellent reaction principle for multiplex detection of

mutations" (p. 607, col. 2). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have adjusted the teachings of Rabbani and David to include the attachment of primers to solid phase supports as taught by Pastinen to arrive at the claimed invention with a reasonable expectation for success.

Response to Arguments

Applicant's arguments filed April 4, 2011 have been fully considered but they are not persuasive.

Applicant traverses the rejection over Rabbani in view of David. Applicant first argues that "David involves the design of primers which perform their intended function in conditions that are completely different from the conditions in which Rabbani's primers are intended to perform their function". Applicant argues that the multiple steps of denaturation depicted in Figure 5 "are critical to form the double stranded folded portions on the left-hand side of the double strand as shown in Figure H" (p. 4 of remarks). Applicant goes on to argue regarding Rabbani. Applicant argues "Rabbani teaches a design of primers that require only one initial thermal denaturation step" (p. 5 of remarks). Applicant also argues "one skilled in the art of designing primers for amplification conditions that involve only one initial thermal denaturation step as taught by Rabbani, would not turn to the design of primers that require thermal heating of the reaction mixture after the amplification reaction has already been initiated..." (p. 5 of remarks).

Next, Applicant turns to Rabbani and argues that "Figure 4 in no way shows a combination of primers" and while Applicant agrees that "in Figure 4, the primer having the

sequence E' and F is the TP", Applicant argues that "the strand having the sequence BCDEF E' shown in steps 2,3,4 is an elongated strand, and is not a primer" and concludes that Figure 4 does not teach a combination of primers (see p. 6-8 of remarks). Applicant argues in conclusion that "Figure 4 of Rabbani shows the use of only one primer and does not disclose or suggest the use of a combination of primers" and "does not provide any other guidance as to the structure of the second primer". Finally, Applicant again argues that "given that David teaches the requirement of reaction conditions that are completely different from those of Rabbani to achieve intended function of their primers, there would not have been a reasonable expectation for success" (p. 8 of remarks).

These arguments have been carefully considered, but are not persuasive. In light of Applicant's arguments which address the secondary reference, David, first, this portion of the arguments will be addressed first, as well. While Applicant's arguments regarding the intended use or function of the primers of David are noted, it is noted in response that the rejection is drawn to a pair of primers, or a product, and not to a method or a product by process claim. Applicant is taking Figure 5 as a whole, when in fact, the FP (fold-back primer) of David is taught in Figure 5a. The fold back primer structure of primer P1 is sufficient to anticipate the second FP primer as claimed. While it is interesting to note that the primer is used in a technique that includes a fold-back portion at either end of the target, that intended use of the primer does not take away from the fact that the fold-back primer is taught specifically by David and it is also noted that this intended use does not teach away from a combination with Rabbani, since the combination of the teachings relies on the FP primer of David and the TP (turn back primer) of

Rabbani and is not directed to the specific format of amplification or primer extension depicted at the conclusion of Figure 5.

Furthermore, while Applicant's arguments against Rabbani are noted and while Applicant is technically correct that a second primer is not depicted in Figure 4, as noted in the motivation statement, "a second sequence at the opposite end of the template or extension product which includes a folded hairpin sequence" is taught in Figure 4. While Applicant focused all of their attention on the bottom extension strand BC'DEFE', this statement in the motivation statement refers to the top strand which includes a folded back sequence which includes in part a portion CB'C', which matches quite well with the claimed fold back portion of the primer DDeCc. While yes, the extended product does not comprise an actual primer, the structure looks similar to what an extension of a fold back primer would look like. For example, look at Figure 3 of the instant invention, where the TP primer begins the reaction and then the FP primer hybridizes and extends, the product of that reaction looks very similar to the teachings of Figure 4. That is what was meant by the portion of the motivation statement. Further, while Applicant's arguments regarding the "second primer" taught by Rabbani not having any detail or structure, it is noted in response, that again details regarding structure were particularly pointed out in the motivation statement: "...as taught by Rabbani, 'the initial primer or nucleic acid construct and the second primer or nucleic acid construct can be the same, or they can be different' (see paragraph 43, p. 8). Therefore, it is clear that Rabbani contemplates and specifically discusses a second primer and considering the teachings of David, it would have been obvious to combine the TP primer of Rabbani with the FP primer of David to arrive at the

claimed invention with a reasonable expectation for success. Applicant's arguments are not persuasive and the rejections are maintained.

Conclusion

No claims are allowed. All claims stand rejected.

This is a continuation of applicant's earlier Application No. 10/583706. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **STEPHANIE K. MUMMERT** whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephanie K. Mummert/
Primary Examiner, Art Unit 1637

SKM